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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,725	11/30/2001	Wely B. Floriano	06618-607002	4307
20985 7590 08/30/2007 FISH & RICHARDSON, PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			EXAMINER WHALEY, PABLO S	
			ART UNIT 1631	PAPER NUMBER
			MAIL DATE 08/30/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/010,725	FLORIANO ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 June 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,6,9-14,16,31,36-42 and 45-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### *REQUEST FOR CONTINUED EXAMINATION*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/25/2007 has been entered.

### *STATUS OF CLAIMS*

Applicant's traversal, filed 06/25/2007, of withdrawn claims 48, 49, 52, and 55 is persuasive, as the Examiner agrees there is no serious burden imposed by searching these claims directed to a system for carrying out the method of claim 1. This restriction is hereby withdrawn for claims 48, 49, 52, and 55. Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are herein under examination. Claims 3, 5, 7, 8, 15, 17-30, 32-35, 43, and 44 have been cancelled. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

### *PRIORITY*

Priority to provisional application 60/213,658, filed 06/23/2000, is acknowledged.

### **CLAIM REJECTIONS - 35 USC § 112, 2<sup>nd</sup> Paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 31, and 48 are rejected for the following reasons. Claims which are directly or indirectly dependent from these claims are also included as rejected herein, due to said dependence.

Claims 1, 31, and 48: The instant claims now recite "further optimizing...by using annealing molecular dynamics including solvation effects." Since the claims do not set forth any steps indicating in what way "annealing molecular dynamics" includes solvation effects, it is unclear what method/process applicant is intending to encompass. Clarification is again requested via clearer claim language. This limitation is broadly interpreted for purposes of applying prior art.

**CLAIM REJECTIONS - 35 USC § 102**

The rejection of claims 1, 2, 4, 9, 11, 12, 16, 29, 31, 36, 37, 39, 40, 46, 47, 50, 51, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by DeWitte et al. (*J. Am. Chem. Soc.*, 1996, Vol.118, p. 11733-11744) is withdrawn for the following reasons.

Applicant's arguments that DeWitte et al. does not teach the same number of steps as required by the instant claims are not persuasive. It is noted that the transitional phrase "comprising", as recited in claims 1, 31, and 48, is open-language and does not exclude additional, unrecited elements or method steps [MPEP 2111.02]. Furthermore, it is well established that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results [See *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930)]. However, applicant's arguments that DeWitte et al. do not teach specifically teach optimization using "annealing molecular dynamics" is persuasive. This rejection is hereby withdrawn.

**Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 6, 9-14, 16, 31, 36-42, and 45-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zou et al (J. Am. Chem. Soc., 1999, Vol. 121, p.8033-8043), in further view of Bassolino et al. (Protein Science, 1996, Vol. 5, p.593-603).

Applicant's arguments that Zou et al. does not teach the same number of steps as required by the instant claims is not persuasive for the following reasons. The transitional phrase "comprising", as recited in claims 1, 31, and 48, is open-language and does not exclude additional, unrecited elements or method steps [MPEP 2111.02]. Furthermore, it is well established that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results [See *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930)]. Applicant's arguments that Zou et al. does not specifically teach optimization using "annealing molecular dynamics" have been considered but are moot in view of the new grounds of rejections.

As set forth in the previous office action mailed 01/24/2007, Zou et al. teaches a computer-assisted method for modeling ligand-receptor binding interactions [Abstract]. In particular, Zou et al. teach the following aspects of independent claims 1, 31, and 48:

- Obtaining structural information from crystal structures to identify binding regions [p.8037, col.1-2, III, Results, § 1].

Art Unit: 1631

- Applying DOCK (i.e. coarse-grain search algorithm) is used to identify 10,000 top force field scoring molecules and rank the selected candidates [p. 8037, col.2, Section 2], and selecting the best scoring conformations based on lowest energy [Table 4]. Furthermore, as DOCK is a well-known as a method of force-field scoring, the Examiner has broadly interpreted DOCK as a teaching for optimization using "molecular mechanics" (See [www.answers.com](http://www.answers.com) definition).
- GB/SA model of solvation for calculating binding energies [p.8034, Col. 1, Section 1].
- Ranking of candidates for selection of optimal conformations based on binding energy [p.8037, Col. 2, Section 2] and [p.8037, Section 6].
- Resulting indicating top scoring candidates from a database [p.8040, Col. 1, ¶ 3] and [Tables 2 and 3] and generation of top 10 orientations with DOCK [Table 4], which equates to outputting a data files of selected conformations as programs inherently output data.
- All above computations are done using software and a Silicon Graphics workstation [Abstract], therefore the Examiner has reasonably interpreted the method and algorithms of Zou et al. as a an implicit teaching for a computer program product and system, as in claims 31 and 48.

Zou et al. also teaches the following aspects of the following dependent claims. Ranking is done known binding regions [p.8037, Col. 2, Section 2], as in instant claim 2. Scoring of ligand molecules is based on the grid spacing of 0.3 Å (first energy function) and distance cutoff of 10Å (second energy function), where orientation (i.e. conformation) minimization is performed and the results are given in Table 1 (page 8037, column 2, lines 1-19 and Table 1), as in instant claims 4-6, and 8. Effective Born radii calculations [p.8036, Col. 2, Section 2] enable spatial



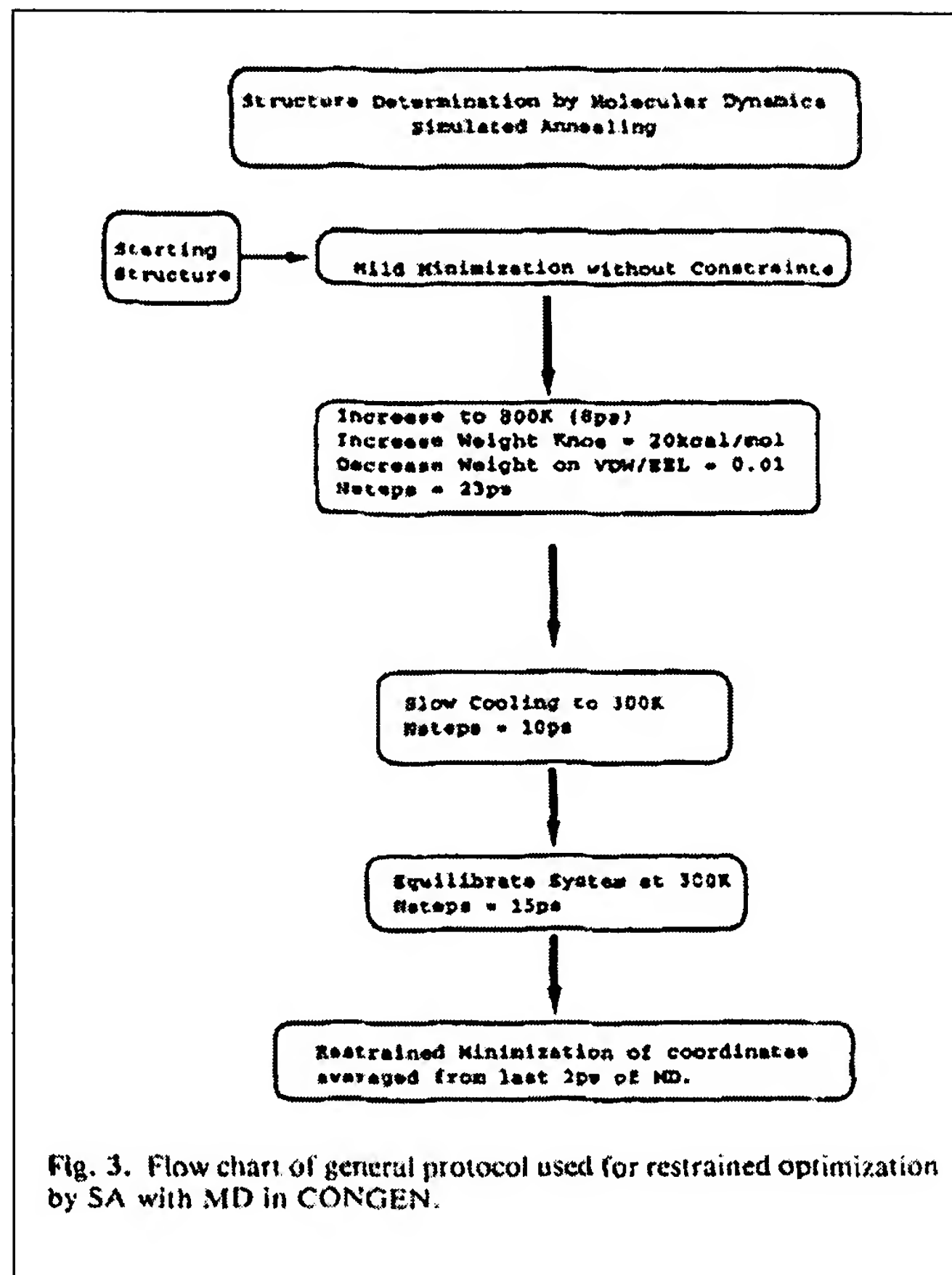
Art Unit: 1631

selection of optimal conformations within an energy grid, wherein the Examiner has broadly interpreted as 'spatial clustering' as in claims 4, 36. Zou et al. discloses a continuum solvent model [p.8035, Section 3] and EQUATIONS 4, 5, and 6 that clearly incorporate surface area into their model, as in instant claims 10, 11, 38, and 39. EQUATION 8 enables calculation of binding energy for each ligand where the binding energies are represented as the difference  $G_{LR} - G_L - G_R$  in solvent (where L= ligand, R=receptor/protein), as in instant claims 12 and 14, and account for binding energy dependence on water [p.8037, Col. 1, ¶2], as in claims 13, 41, and 49. Binding energy for each ligand is calculated by taking the difference in the ligand energy of ligand in solvent and in receptor (page 8035, columns 2, §3 and §4 to page 8036, column 1), as in instant claims 12, 40, and 42. Zou et al. disclose methods directed to globular protein and the calculation of dielectric constant of said protein in water (page 8035, column 1, lines 3-12), as in instant claim 16. Zou et al. teach the treatment of solvent molecules in molecular dynamics simulations (page 8033, column 2, lines 14-15), where unoccupied embedded space between ligand and the receptor (empty volume) is penalized and energy minimization is performed with DOCK force field scoring (i.e. full atom force field), as in instant claims 9 and 37. The GB/SA model computes ligand binding energies wherein the parameters are approximated by a linear dependence on the solvent-accessible surface area and dielectric properties around the binding site as directed to the unoccupied embedded space (page 8034, 11. Method §, column 2, to page 8035, column 1, line 26). The first set of parameters yields the best fit binding energies six inhibitors (subset). TMP and MTX rank no. 1 and no. 2 among top scoring 10,000 ACD molecules for dhfr (page 8040, column 1, lines 10-19), as in instant claim 45. Scoring functions based on subtraction of free energies [EQUATIONS 15 and 16, p.8037], as in claims 46 and 47.



Zou et al. do not specifically teach optimization using “annealing molecular dynamics including solvation effects”, as in claims 1, 9, 31, 37, 48, 50, 51, and 52. However, Zou et al. teach a continuum solvent model and molecular dynamics simulations (page 8033, column 2, lines 14-15), which suggests the combination of molecular dynamic computations including solvation effects. Zou et al. do not specifically teach the “calculated percentage of ligand surface area” limitation of claims 6, 45, and 56. However, EQUATION 11 clearly calculates the change in hydrophobic and total solvent-accessible surface areas for selecting optimal conformations [p.8036] and uses predefined grids for evaluating protein-ligand binding based on Born-radii areas [Fig. 2]. Thus, it would have been well within the ordinary capabilities of one skilled in the art select the best conformations based on percentage calculations of ligand surface area buried within a protein. Zou et al. do not specifically teach Monte Carlo methods, as in claims 53-55, however Monte Carlo simulations are taught as obvious methods for simulation of binding interactions. Thus, it would have been well within the ordinary capabilities of one skilled in the art select the best conformations using Monte Carlo algorithms.

Bassolino et al. teach a program (CONGEN) for molecular structure generation that uses several search algorithms including MD with the CHARMM (full atom force field) potential energy function [p.594, Col. 1, ¶4], as well as simulated molecular dynamics (SA-MD) procedures for generating 3-D protein structures [Fig. 3, below], as in claims 1, 9, 31, 37, 48, 50, 51, and 52. Each of the final structures was further refined by energy minimization in CONGEN and resulting coordinates are stored for analysis [p.602, Col. 2, ¶2].



Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the SA-MD optimization algorithm of Bassolino et al. for identifying optimal ligand conformations according to the method Zou et al., as computational techniques for determining protein structures using docking algorithms that utilize simulated annealing are well known in the art [Bassolino et al., p.593], resulting in the practice of the instant claimed invention with predictable results. One of ordinary skill in the art would have been motivated to use the SA-MD optimization procedure for the improvements it provides over other programs by allowing users to control weights on individual constraints throughout the annealing procedure [Bassolino et al., p.594, Col. 2, ¶ 1].

Claims 1, 2, 9, 31, 37, 48, and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vieth et al. (Journal of Computational Chemistry, 1998, Vol. 19, No. 14, p.1623-1631), in view of Moyna et al. (Biopolymers, 1999, Vol. 49, p.403-413).

The instant invention is directed to a method, computer program product, and system for identifying one or more ligand conformations that bind to a protein.

Vieth et al. teach methods for identifying one or more ligand conformations that bind to a protein including molecular dynamics (MD), Monte Carlo (MC), and genetic algorithm (GA) methods [Abstract]. More specifically, Vieth et al. teach the following aspects of the instant invention:

- Obtaining structural information and binding regions from known ligand-receptor complexes in a database [p.1624, Col. 2, ¶2], as in claims 1, 2, 31, and 48.
- Three-stage docking protocol wherein the first stage identifies a plurality of binding conformations to known structures using docking algorithms including Monte Carlo (i.e. coarse-grained docking algorithm) [Table III], the second stage includes annealing for MC and MD for finding local minima, and the third stage further minimizes structures based on temperature quenching [p.1626, Col. 2, ¶ 1], as in claims 1, 31, 48, and 53-55.
- Calculating individual and mean binding energies of lowest energy structures (i.e. preferred conformations) [p.1629, Col. 1, ¶ 2] and statistical ranking of structures preferred structures (i.e. within 1 angstrom) [Table II], as in claims 1, 31, and 48.
- Outputting the fraction of docked structures within 1 angstrom RMSD of the crystal structure [Table III] wherein all computations are done via computer workstations [p.1631, Col. 1, ¶ 2], which is an implicit teaching for outputting data files of selected

Art Unit: 1631

ligand-protein conformations having lowest calculated binding energy as in claims 1, 31, and 48.

- All above computations are done using software and a Silicon Graphics workstation [p.1631, Col. 1], therefore the Examiner has reasonably interpreted the method and algorithms of Zou et al. as a an implicit teaching for a computer program product and system, as in claims 31 and 48.

Vieth et al. do not teach specifically teach optimization using “annealing molecular dynamics including solvation effects”, as in claims 1, 9, 31, 37, 48, 50, 51, and 52. However, Vieth et al. clearly teach annealing methods and energy functions using distance-dependent dielectrics [p.1625, Col. 1, ¶2] ,which suggests the use of method for simulation of solvent effects (which are based on dielectric constants (See [www.answers.com](http://www.answers.com) definition for solvation)).

Moyna et al. teach computer assisted methods for molecular modeling wherein conformer sets are generated by restrained simulated annealing experiments running on computer systems [p.411, Col. 2]. The AMBER force field program is used to simulate solvent effects. Specific ranges were assigned for ranking interactions. Simulated annealing experiments are followed by minimization of the resulting structures to an energy gradient below a specific threshold [p.412, Col. 1]. Initial conformations used in annealing experiments were generated by distance geometry and optimized for lowest energy. Molecular dynamics are performed using TINKER program on a supercomputer. AMBER 95 force field and charges are used and include implicit GB/SA solvation started from the lowest energy conformer obtained by simulated annealing. A total of 5000 structures are generated. Structure analysis was performed using MSS [p.412, Col. 1]. Therefore, Moyna et al. provide evidence for optimization based on

Art Unit: 1631

annealing molecular dynamics including solvation effects and energy minimization of conformations 1, 9, 31, 37, 48, 50, 51, and 52.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the SA-MD optimization algorithm of Moyna et al. for identifying optimal ligand conformations according to the method Vieth et al., as combined techniques for establishing protein structures using docking algorithms that utilize simulated annealing are well known in the art [Vieth et al. p.1624], resulting in the practice of the instant claimed invention with predictable results. The motivation to use the SA-MD optimization procedure is provided by Moyna et al., who suggest their model is an efficient method for MD simulations that could be applied with similar results to other small peptides for designing novel environmentally safe insect management agents [p.411, Conclusions].

## CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1631

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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